INTERNAL MEDICINE

□ CASE REPORT □

A Case of Intravascular Large B-cell Lymphoma (IVLBCL) with no Abnormal Findings on Chest Computed Tomography Diagnosed by Random Transbronchial Lung Biopsy

Norihito Kaku[1], Masafumi Seki[1], Seiji Doi[1], Tomayoshi Hayashi[2], Daisuke Imanishi[3], Yoshifumi Imamura[1], Shintaro Kurihara[1], Taiga Miyazaki[1], Koichi Izumikawa[1], Hiroshi Kakeya[1], Yoshihiro Yamamoto[1], Katsunori Yanagihara[1,2], Takayoshi Tashiro[1] and Shigeru Kohno[1]

Abstract

A 58-year-old woman was admitted with refractory fever despite receiving broad-spectrum antibiotics. She had hypoxemia, severe anemia, elevated levels of serum lactic dehydrogenase and soluble interleukin-2 receptor, and a positive direct Coombs test, which suggested an underlying autoimmune hemolytic anemia (AIHA). Chest computed tomography (CT) showed no abnormal findings, but she had hypoxia, and her alveolar-arterial oxygen difference (A-aDO_2) was increased. A random transbronchial lung biopsy (TBLB) was performed, and pathological analysis showed massive proliferation of tumor cells in the lumina of the small vessels. Intravascular large B-cell lymphoma (IVLBCL) was diagnosed, and her general status improved after chemotherapy.

Key words: autoimmune hemolytic anemia (AIHA), computed tomography, fever of unknown origin (FUO), intravascular large B-cell lymphoma (IVLBCL), rituximab, transbronchial lung biopsy (TBLB)

(Intern Med 49: 2697-2701, 2010)
(DOI: 10.2169/internalmedicine.49.3986)

Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare type of extranodal large B-cell lymphoma that is characterized by proliferation of lymphoma cells within the lumina of small blood vessels and capillaries, and it was recently listed as a rare subtype of diffuse large B-cell lymphoma in the World Health Organization (WHO) classification (1-5). Clinical symptoms occur when lymphoma cells proliferate within the lumina of the small vessels. IVLBCL often shows symptoms related to the nervous system and skin, but abnormal findings related to lymph nodes, bone marrow, and other solid organs are relatively rare in Western countries (6-8).

IVLBCL in the lung is often suspected because of hypoxia and abnormal chest findings on chest x-ray and/or computed tomography (CT), and it is usually diagnosed pathologically by transbronchial lung biopsy (TBLB), skin biopsy from the site of a rash, or a peripheral nerve biopsy when neuritis is present (9-11).

The case of an IVLBCL patient who had no abnormal chest findings on both chest x-ray and CT, though dyspnea/hypoxia was present, and in whom the diagnosis was made by TBLB, is presented. She also might have had autoimmune hemolytic anemia (AIHA), which is rarely described as a complication of IVLBCL.

[1]The Second Department of Internal Medicine, Nagasaki University Hospital, Nagasaki, [2]Department of Clinical Laboratory, Nagasaki University Hospital, Nagasaki and [3]Department of Hematology, Molecular Medicine Unit, Atomic Bomb Disease Institute, Nagasaki University, Nagasaki
Received for publication May 23, 2010; Accepted for publication September 13, 2010
Correspondence to Dr. Masafumi Seki, seki@nagasaki-u.ac.jp

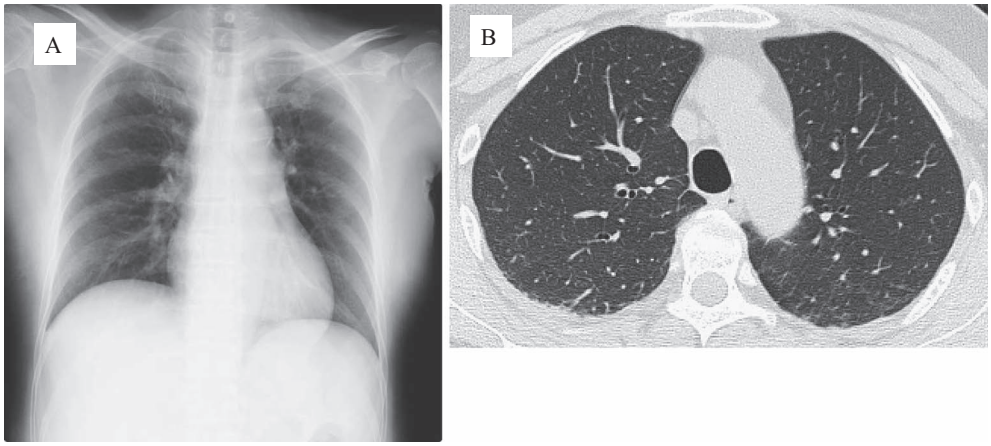

Figure 1. **Chest X-ray (A), and CT scan (B). No abnormal shadows were seen in either the X-ray or CT scan.**

Case Report

A 58-year-old woman who had been complaining of persistent cough and intermittent high fever as high as 40°C for 2 weeks was admitted to a community hospital. Her chest x-ray showed no abnormal shadows, and hypoxia was absent. Lymph nodes were not palpable, and liver function tests and spleen size were normal. However, laboratory data showed anemia (hemoglobin, 10.1 g/dL) and elevated serum lactic dehydrogenase (LDH) (570 IU/L) and C-reactive protein (CRP) (10.3 mg/dL) levels. A concomitant viral and bacterial/rickettsial infection was suspected, and administration of broad-spectrum antibiotics, including quinolones, tetracyclines, and carbapems, was started.

However, her symptoms, anemia, and general condition deteriorated, and she was admitted to our hospital as a case of fever of unknown origin (FUO) after antibiotic administration for 2 weeks. On admission, high fever persisted, and dyspnea and hypoxia (SpO_2, 88% on room air) were present.

Physical examination was normal. Specifically, chest auscultation was normal, and there were no skin lesions, lymphadenopathy, or neurological signs. However, laboratory findings showed severe inflammation and anemia (hemoglobin: Hb, 8.1 g/dL), and mild jaundice and hepatosplenomegaly were evident. Although antibodies against red blood cells were not measured, haptoglobin deficiency, elevated reticulocytes (3.8%), indirect bilirubin (1.4 mg/dL), and urinary urobilinogen (3.0 mg/dL) and a positive direct Coombs test were also found; autoimmune hemolytic anemia (AIHA) was diagnosed, and blood transfusions had to be temporarily performed before steroid administration because the primary underlying diseases had not yet been diagnosed, the anemia was rapidly worsening (Hb 5.8 g/dL), and the patient developed shock. Drug-induced hemolytic anemia was excluded because anemia (Hb 10.1 g/dL) had already been found at a periodic medical examination one month prior to the administration of antibiotics.

Infection, collagen diseases, drug-induced, and lymphoproliferative diseases were suspected as the primary disease causing the high fever and AIHA. However, microbiological examinations, such as sputum, urine, and blood cultures, were negative, and the evaluation for collagen disease was unremarkable; rheumatoid factor, antinuclear antibodies, and C- and P- antineutrophil cytoplasmic antibodies (ANCA) were negative. Examinations for a broad range of serum tumor markers were all negative, except for a high level of soluble interleukin-2 receptor (sIL2-R) (3,699 U/mL), which strongly suggested the possibility of a malignant lymphoma, though no abnormal chest findings and lymph node swelling were present (Fig. 1A, B). Bone marrow aspiration was performed, showing a slightly hypoplastic marrow, but no lymphoma cells were observed.

We suspected IVLBCL because of her general symptoms and evidence of hypoxia [pH 7.513, PaO_2 56.0 mmHg, $PaCO_2$ 28.7 mmHg on room air, along with an increased alveolar-arterial oxygen difference (A-aDO_2) of 58 mmHg]. Skin and lung biopsies were performed, though there were no findings related to these organs. The skin and nerve biopsy results were normal, but the randomly obtained TBLB samples from the right lung showed lymphoma cells within small pulmonary arteries, veins, and capillaries, but not outside the vessels (Fig. 2A, C). Intravascular cells were positive for CD20 (L26) (Fig. 2B, D) and CD79a (data not shown), which are B-cell markers, and they were negative for CD3 and CD4, which are T-cell markers. IVLBCL was the final diagnosis.

Systemic chemotherapy, consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP), was started immediately after the final definitive diagnosis of IVLBCL. Administration of rituximab with prophase therapy is thought to be safe despite severe pulmonary complications related to rituximab infusion as an initial treatment (12). In this case, no severe adverse effects occurred, and the condition of the patient improved.

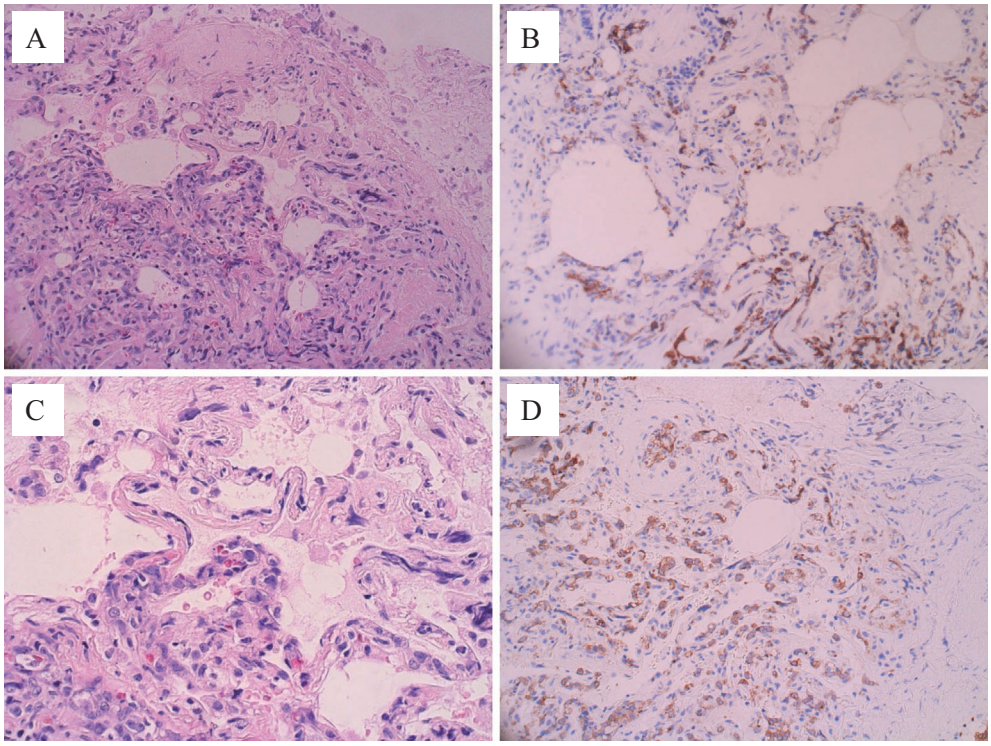

Figure 2. **Transbronchial lung biopsy (TBLB) specimen demonstrates invasion of many atypical lymphoid cells into the capillary vessels of the alveolar septae. (A) and (C): Hematoxylin and Eosin staining, (B) and (D): Immunohistochemical staining for CD20. (A) and (B), ×200; (C) and (D), ×400 magnification.**

Discussion

IVLBCL was first described by Pfleger and Tappeiner in 1959 (6), and over 300 cases have been reported to date. Symptoms such as fever, night sweats, and weight loss are seen in the majority of patients, and these are thought to be partially caused by blood flow disturbances due to proliferation of lymphoma cells within the lumina of the small vessels (2, 3, 10, 13). However, a relationship between B symptoms and CD5+ cells, thrombocytopenia, and hemophagocytosis due to humoral factors, such as IL-6 and macrophage colony-stimulating factors, has been reported (4, 13, 14)

In Western countries, IVLBCL patients usually show symptoms of central nervous system (CNS) and skin involvement (1, 6-8, 13). In contrast, IVLBCL patients in Japan usually show fever, hepatosplenomegaly, and thrombocytopenia in 73-100% of cases, very rarely with CNS and skin involvement (2, 11, 15). Furthermore, hemophagocytotic syndrome and bone marrow involvement are also common in IVLBCL patients in Japan. The present patient had high fever, developed splenomegaly and, finally, hypoxia, though no CNS and skin symptoms were present, as in other cases in Japan.

Recent reports revealed that about one-quarter of IVLBCL patients in Japan had neurological symptoms at the time of diagnosis (14). Although the accurate evaluation of CNS involvement might be difficult because most patients with neurological symptoms did not undergo CNS biopsies in Japan, CNS involvement might not be thought to be rare in Japanese IVLBCL patients, given the high incidence of CNS relapse (16).

In addition, skin involvement in IVLBCL patients in Japan might be under evaluation, as shown by a recent report of random skin biopsies (10). In this case, a random skin biopsy of the patient's left thigh was performed, and two samples were obtained. Unfortunately, no abnormal lesions were found, but it was reported that skin is a safe and useful site for biopsy, and all specimens from healthy skin showed histological features of IVLBCL (10). Histologically, most of the affected vessels were located in the hypodermis or in hypodermic adipose tissue, whereas vessels in the dermis were often spared. Further investigations are needed.

Moreover, AIHA, which has been rarely reported as a complication of IVL, was found in this case. Sallah et al reported that, of 517 non-Hodgkin lymphoma patients, there were 16 (3%) AIHA patients (17). Among the 16 AIHA patients, 2 patients were diagnosed as having diffuse large B cell lymphoma. These results also support the rare description of AIHA as a complication of IVLBCL. Although similar phenomena have been described in patients with solid tumors, attempts to clarify their pathogenic mechanisms have concentrated mainly on patients with CD5+ or mature B-cell malignancies (17-19).

IVLBCL is often suspected on the basis of clinical symptoms and laboratory data, such as elevated serum LDH and

Table 1. Summary of Reported IVL Diagnosed by TBLB

No.	Age	Sex	Country	Chief complaint	Chest CT	Other image	Therapy	Outcome	References
1	56	M	Japan	Fever	Diffuse small nodules	Ga scintigraphy	CHOP with BLM	PR	21
2	58	M	USA	Fever, dyspnea	No abnormal findings	none	CHOP	CR	7
3	60	M	Japan	Fever, cough	Centrilobular nodules	Ga scintigraphy	CHOP	CR	22
4	53	F	Japan	Fever, cough	Ground glass opacities	none	CHOP	CR	11
5	63	M	USA	Fever, dyspnea	Mosaic attenuation consistent with air trapping	none	CHOP	PR	23
6	65	M	Japan	Fever, dyspnea	Reticulonodular shadows	Lung blood flow scintigraphy	CHOP	CR	24
7	71	M	Japan	Fever	Ground glass opacities	Lung blood flow scintigraphy	VEPA	PR	24
8	65	M	Japan	Dyspnea, dementia	Consolidation and swelling of hilar lymph node	FDG-PET	CHOP	CR	15
9	49	F	Singapore	Fever, cough	Ill-defined interstitial infiltrates	none	DHAP	PR	9
10	68	F	Japan	Fever, dyspnea	Wandering infiltrates	Ga scintigraphy	Modified CHOP	CR	25
11	72	F	Japan	Fever, cough	Ground glass opacities	Ga scintigraphy	R-CHOP	CR	26
12	45	M	Japan	Fever	No abnormal findings	Ga scintigraphy	R-CHOP	CR	27
13	73	M	Japan	Fever, dyspnea, purpuralike skin	Interstitial shadow	none	R-CHOP	CR	10
14	65	M	Japan	Fever, dyspnea	Interstitial shadow	none	R-CHOP	CR	10
15	54	F	Japan	Fever, dyspnea	Ground glass opacities	none	R-CHOP	CR	28
16	46	M	Japan	Fever	Diffuse small nodules	none	R-CHOP	CR	28
17	54	F	Japan	Dyspnea,	Centrilobular opacities	FDG-PET	R-CHOP	CR	29
18	39	M	Japan	dyspnea	No abnormal findings	FDG-PET	R-CHOP	CR	2
19	50	F	Japan	Fever, anorexia, edema, muscular pain	No abnormal findings	FDG-PET	R-CHOP	CR	3
20	58	F	Japan	Fever, cough	No abnormal findings	FDG-PET	R-CHOP, CHASER	CR	This case

s-IL2R levels, but antemortem diagnosis of this disease is often difficult when CNS or skin involvement is absent. Although lymphoma cell invasion of the lung was observed at autopsy in almost all cases (20), there have been only 19 cases diagnosed by TBLB (Table 1) (7, 9-11, 15, 21-29). In many cases, chest CT revealed interstitial infiltrates, patchy consolidations, or ground glass opacities, but there have been only three cases in which chest CT showed no abnormal findings, as in our case. Despite the presence of dyspnea and hypoxia, chest radiography and CT may show no abnormal findings and might be nonspecific (3).

Although the lung is not a common site used to make the diagnosis of IVLBCL, autopsies have revealed changes in the lung in approximately 60% of cases (4, 8). TBLB is one of the most useful methods to diagnose IVLBCL, and thoracoscopic lung biopsy and open lung biopsy have also been reported as promising for diagnosing IVLBCL with lung involvement (3). It was reported that not only the present case, but also other cases in which abnormal findings were absent or less were ultimately diagnosed as having IVLBCL (2, 7, 28). These data also strongly suggested that random TBLB is necessary for diagnosis of IVLBCL, as in the present case, despite the absence of abnormal findings on chest x-ray and CT.

In addition, respiratory function tests might also be useful for detecting chest abnormalities, because IVL BCL is known as one of the causative diseases of severe hypoxia with increased A-aDO_2 and decreased diffusing capacity, though both obstructive and restrictive disturbances were absent or slight, as previously reported (11). Unfortunately, we could not perform this test because of the patient's poor condition.

Recently, FDG-PET has been reported and established as a helpful procedure for the diagnosis of IVLBCL, whereas gallium (Ga) scintigraphy has not been performed routinely in clinical practice (2, 15). Kitanaka et al reported a case in which neither CT nor Ga scintigraphy could reveal the presence of disease in the lung, but FDG-PET revealed diffuse pulmonary FDG-accumulation (3). We could not perform FDG-PET early because of the patient's very poor general status and her unwillingness to be transported to another hospital, but FDG-PET should be performed for the differential diagnosis of FUO and hypoxia cases, in which IVLBCL should be strongly suspected.

In conclusion, a case of IVLBCL was diagnosed by random TBLB, in the absence of abnormal findings on chest x-ray and CT, though hypoxia and dyspnea eventually developed. The patient was admitted with FUO and was found to have AIHA. IVLBCL should be considered in such cases, and random TBLB and FDG-PET should be performed early to make the diagnosis.

References

1. Sheibani K, Battifora H, Winberg CD, et al. Further evidence that "malignant angioendotheliomatosis" is an angiotropic large-cell lymphoma. N Engl J Med **314**: 943-948, 1986.

2. Kotake T, Kosugi S, Takimoto T, et al. Intravascular large B-cell lymphoma presenting pulmonary arterial hypertension as an initial manifestation. Intern Med **49**: 51-54, 2010.

3. Kitanaka A, Kubota Y, Imataki O, et al. Intravascular large B-cell lymphoma with FDG accumulation in the lung lacking CT/(67) gallium scintigraphy abnormality. Hematol Oncol **27**: 46-49, 2009.

4. Murase T, Yamaguchi M, Suzuki R, et al. Intravascular large B-cell lymphoma (IVLBCL): a clinicopathologic study of 96 cases with special reference to the immunophenotypic heterogeneity of CD5. Blood **109**: 478-485, 2007.

5. Nakamura S, Ponzoni M, Campo E. Intravascular large B-cell lymphoma. In: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Swerdlow SH, Campo E, Harris NL, et al, Eds. IARC Press, Lyon, France, 2008: 252-253.

6. Pfleger L, Tappeiner J. On the recognition of systematized endotheliomatosis of the cutaneous blood vessels (reticuloendotheliosis) Zur Kenntnis der systemisdien Endotheliomatose der cutanen Blutgefasse. Hautarzt **10**: 359-363, 1959 (in German).

7. Demirer T, Dail DH, Aboulafia DM. Four varied cases of intravascular lymphomatosis and a literature review. Cancer **73**: 1738-1745, 1994.

8. Snyder LS, Harmon KR, Estensen RD. Intravascular lymphomatosis (malignant angioendotheliomatosis) presenting as pulmonary hypertension. Chest **96**: 1199-1200, 1989.

9. Goh SG, Chuah KL, Tan PH. Intravascular lymphomatosis of the lung and liver following eyelid lymphoma in a Chinese man and review of primary pulmonary intravascular lymphomatosis. Pathology **34**: 82-85, 2002.

10. Asada N, Odawara J, Kimura S, et al. Use of random skin biopsy for diagnosis of intravascular large B-cell lymphoma. Mayo Clin Proc **82**: 1525-1527, 2007.

11. Takamura K, Nasuhara Y, Mishina T, et al. Intravascular lymphomatosis diagnosed by transbronchial lung biopsy. Eur Respir J **10**: 955-957, 1997.

12. Wu SJ, Chou WC, Ko BS, Tien HF. Severe pulmonary complications after initial treatment with Rituximab for the Asian-variant of intravascular lymphoma. Haematologica **97**: 141-142, 2007.

13. Ferreri AJ, Campo E, Seymour JF, et al; International Extranodal Lymphoma Study Group (IELSG). Intravascular lymphoma: clinical presentation, natural history, management and prognostic factors in a series of 38 cases, with special emphasis on the 'cutaneous variant'. Br J Haematol **127**: 173-183, 2004.

14. Murase T, Nakamura S, Kawauchi K, et al. An Asian variant of intravascular large B-cell lymphoma: clinical, pathological and cytogenetic approaches to diffuse large B-cell lymphoma associated with haemophagocytic syndrome. Br J Haematol **111**: 826-834, 2000.

15. Kawamura T, Sando Y, Tajima S, et al. Pulmonary intravascular lymphoma complicated with *Pneumocystis carinii* pneumonia: a case report. Jpn J Clin Oncol **31**: 333-336, 2001.

16. Shimada K, Murase T, Matsue K, et al; for the IVL Study Group in Japan. Central nervous system involvement in intravascular large B-cell lymphoma: A retrospective analysis of 109 patients. Cancer Sci **101**: 1480-1486, 2010.

17. Sallah S, Sigounas G, Vos P, Wan JY, Nguyen NP. Autoimmune hemolytic anemia in patients with non-Hodgkin's lymphoma: characteristics and significance. Ann Oncol **11**: 1571-1577, 2000.

18. Kipps TJ, Carson DA. Autoantibodies in chronic lymphocytic leukemia and related systemic autoimmune diseases. Blood **81**: 2475-2487, 1993.

19. Gabay C, Ben-Bassat H, Schlesinger M, Laskov R. Somatic mutations and intraclonal variations in the rearranged Vkappa genes of B-non-Hodgkin's lymphoma cell lines. Eur J Haematol **63**: 180-191, 1999.

20. Corby TB. Malignancies in the lung and pleura mimicking benign processes. Sem Diag Pathol **12**: 30-44, 1995.

21. Wakamatsu K, Komori M, Nagata N, Kumazoe H, Kajiki A, Kitahara Y. Two cases of intravascular lymphomatosis diagnosed by transbronchial lung biopsy. Nihon Kokyuki Gakkai Zasshi (The Journal of Japanese Respiratory Society) **47**: 875-880, 2009 (in Japanese).

22. Okubo H, Yoshida T, Ohta K, et al. A case of pulmonary intravascular lymphoma treated with CHOP chemotherapy plus Rituximab. Jpn J Cancer Chemother **32**: 553-556, 2005 (in Japanese).

23. Walls JG, Hong YG, Cox JE, et al. Pulmonary intravascular lymphomatosis: presentation with dyspnea and air trapping. Chest **115**: 1207-1210, 1999.

24. Honda N, Machida K, Kamano T, et al. Gallium scintigraphy in neoplastic angioendotheliosis of the lung. Clin Nucl Med **16**: 43-46, 1991.

25. Inoue K, Rikimaru S, Ueno K, Kurumaya H. A case of intravascular lymphomatosis presenting primary in the lung. A case of intravascular lymphomatosis presenting primary in the lung. Japanese Journal of Clinical Radiology **40**: 1173-1175, 1995 (in Japanese).

26. Taura Y, Yamazaki H, Katou T. Two cases of intravascular lymphomatosis diagnosed antemortem by transbronchial lung biopsy. Nihon Kokyuki Gakkai Zasshi **38**: 34-38, 2000 (in Japanese).

27. Okawa Y, Usui N, Uno S, Dobashi N, Kasama K, Kobayashi M. Itravascular large B cell lymphoma with migratory local high density shadow by chest CT and diagnosed by transbronchial lung biopsy. Rinsho Ketsueki **43**: 567-572, 2002 (in Japanese).

28. Iwagami Y, Sumitani M, Imahashi Y, et al. A case of intravascular lymphomatosis with no abnormal findings on chest computed tomography and with diffuse pulmonary uptake of 67Ga on scintigraphy. Nihon Kokyuki Gakkai Zasshi **44**: 923-927, 2006 (in Japanese).

29. Shinoda H, Maejima A, Shimizu K, Onaka A, Boku T, Oyamada Y. A case of intravascular lymphoma with diffuse centrilobular opacities. Nihon Kokyuki Gakkai Zasshi **48**: 76-78, 2010.